*DOI:*
10.1136/thoraxjnl-2015-207315

*Document Version*
Peer reviewed version

**Title:** The validity of health-related quality of life questionnaires in bronchiectasis: a systematic review and meta-analysis

**Authors:** Arietta Spinou[1,2], MSc; Konstantinos C. Fragkos[3], PhD; Kai Lee[4], MD; Caroline Elston[4], MD; Richard J. Siegert[5], PhD; Michael R. Loebinger[6], PhD; Robert Wilson[6], MD; Rachel Garrod[7], PhD; and Surinder S Birring[1], MD

**Author affiliations:**

[1]King's College London, Respiratory Medicine, Division of Asthma, Allergy and Lung Biology, London, UK

[2]Physiotherapy Department, Royal Brompton Hospital, London, UK

[3]University College London (UCL), Division of Medicine, London, UK

[4]King's College Hospital, Adult Cystic Fibrosis Unit, Denmark Hill, London, UK

[5]Auckland University of Technology (AUT), School of Public Health and Psychosocial Studies and School of Rehabilitation and Occupation Studies, Auckland, NZ

[6]Host Defence Unit, Royal Brompton Hospital, London, UK

[7]King's College London, Therapies, Denmark Hill Campus, London, UK

**Corresponding author and request for reprints to:**

Surinder S. Birring

E-mail: surinder.birring@nhs.net

King's College London, Division of Asthma, Allergy and Lung Biology

Denmark Hill, London

SE9 5RS

UK

Tel: (+44) 203 299 4630

Fax: (+44) 203 299 3791

**Keywords:** health-related quality of life, questionnaire, bronchiectasis, systematic literature review, meta-analysis

**Manuscript word count** (excluding title page, abstract, references, figures and tables)**: 3,910**

**Prior publication:** Part of this work has been presented as abstracts at the European Respiratory Society International Congress 2014.

## KEY MESSAGES

**What is the key question?** Which health-related quality of life questionnaires are used in bronchiectasis and what is the evidence for their validity?

**What is the bottom line?** Despite differences in the construct of frequently used questionnaires St George's Respiratory Questionnaire, Leicester Cough Questionnaire and Quality of Life - Bronchiectasis, there is good evidence to support their validity, internal reliability and repeatability.

**Why read on?** This article provides an in depth review of the evidence for the validity of HRQOL questionnaires and their association with commonly used clinical outcome parameters; this may help investigators to select the most appropriate tool for their purpose.

## LIST OF ABBREVIATIONS:

| | |
|---|---|
| CAT | Chronic Obstructive Pulmonary Disease Assessment Tool |
| CI | Confidence Intervals |
| COPD | Chronic Obstructive Pulmonary Disease |
| CQLQ | Cough Quality of Life Questionnaire |
| CRDQ | Chronic Respiratory Disease Questionnaire |
| CT | Computed Tomography |
| EuroQOL | Euro Quality of Life |
| HRQOL | Health-Related Quality of Life |
| ICC | Intraclass Correlation Coefficient |
| QOL-B | Quality of Life - Bronchiectasis |
| LCQ | Leicester Cough Questionnaire |
| SF-36 | Medical Outcomes Study 36-item Short-Form Health Survey |
| SGRQ | St George's Respiratory Questionnaire |
| SNOT-20 | 20-Item Sino-Nasal Outcome Test |

## ABSTRACT

**Background:** Health-related quality of life (HRQOL) is impaired in bronchiectasis. A range of HRQOL questionnaires have been used to assess HRQOL in bronchiectasis. A systematic review was conducted to evaluate the psychometric properties of these questionnaires. This included a meta-analysis to assess associations between HRQOL and clinical measures.

**Methods:** Five electronic databases were searched. Studies eligible for inclusion were those that investigated the validity of HRQOL questionnaires and/or their association with other outcomes in adults with bronchiectasis. Patients with cystic fibrosis were excluded. The identified questionnaires were assessed for convergent, discriminant and cross-cultural translation validity; missing data, floor and ceiling effects, internal consistency and test-retest reliability. A meta-analysis was conducted to estimate the strength of associations between HRQOL and clinical measures.

**Results:** From 1,918 studies identified, 43 studies were included in the systematic review, of which 38 were suitable for the meta-analysis. Nine HRQOL questionnaires were identified, with the most widely used being: St George's Respiratory Questionnaire, Leicester Cough Questionnaire, Quality of Life - Bronchiectasis and Short Form 36. HRQOL questionnaires had moderate to good internal consistency and good test-retest reliability. Only 8 of 18 studies that used translated HRQOL questionnaires reported or referred to the validity of the translated questionnaire. There was a stronger correlation between HRQOL and subjective outcome measures, such as cough (r=0.57), dyspnoea (r=0.55) and fatigue (r=0.42) compared to objective measures; exercise capacity (r=-0.41), $FEV_1$% predicted (r=-0.31) and extent of bronchiectasis in computed tomography scan (r=0.35); all $p<0.001$.

**Conclusions:** This review supports most HRQOL questionnaires used in bronchiectasis have good psychometric properties. There was a weak to moderate association between HRQOL

and objective outcome measures. This supports that HRQOL questionnaires assess a unique aspect of health not captured by objective measures.

**Abstract word count:** 250

# INTRODUCTION

The assessment of health-related quality of life (HRQOL) is important in chronic disease as it evaluates the overall impact on health from the patients' perspective. Bronchiectasis is a persistent or progressive condition characterised by dilated thick-walled bronchi.[1] Symptoms of bronchiectasis include sputum production, cough, haemoptysis, dyspnoea and fatigue, which are worse during exacerbations. HRQOL is impaired in bronchiectasis.[2] A range of tools have been used to assess HRQOL in bronchiectasis. These include generic tools such as the Medical Outcomes Study 36-Short-form Health Survey (SF-36), organ-specific tools such as the St George's Respiratory Questionnaire (SGRQ) and Leicester Cough Questionnaire (LCQ) and the condition-specific Quality of Life – Bronchiectasis (QOL-B).[3-6] The comparative validity of HRQOL questionnaires used to assess bronchiectasis has not been investigated; such a review may inform investigators and clinicians about the choice of HRQOL questionnaires available and their validity. The aim of this systematic literature review was to evaluate the psychometric properties of questionnaires used to assess HRQOL in bronchiectasis. This included a meta-analysis to assess the associations of HRQOL with other clinical measures.

# METHODS

## Study eligibility criteria

The inclusion criteria were: empirical studies of adult patients (≥16 years old) with bronchiectasis, studies reporting the psychometric properties of generic and disease specific HRQOL questionnaires, and/or the association of HRQOL with other clinical measures. The diagnosis of bronchiectasis was established using clinical and/or radiological features. The

review was limited to studies reporting in English language. Studies investigating acute exacerbations were included if they met the inclusion criteria. Studies investigating mixed populations such as adult/paediatric and non-cystic fibrosis/cystic fibrosis bronchiectasis were included if the findings reported were distinguishable by age/disease category. The exclusion criteria were: diagnosis of cystic fibrosis and review articles (used only to identify further references). Clinical trials that did not investigate HRQOL psychometric properties as their primary purpose were excluded. Studies using cognitive interview or focus group methodology that did not include HRQOL questionnaires were also excluded.

The psychometric properties considered included convergent and discriminant validity (relationship with other clinical measures according to expectations), internal consistency (α Cronbach's coefficient: extent to which the items of a questionnaire are interrelated), test-retest reliability (repeatability during a clinically stable period), missing data, floor (minimum score) and ceiling (maximum score) effects. The validity of translated HRQOL questionnaires was evaluated by assessing if forward/backward translation, cognitive interviews, internal consistency and reliability was reported. For the purposes of this review we refer to the following definition of HRQOL: "the perception of the impact of health on an individual's contentment or satisfaction with life in areas they consider important".[7]

**Search strategy and terms**

PRISMA guidelines and SIGN methodology checklist for systematic reviews and meta-analyses were used.[8,9] The search was conducted in 5 electronic databases: Embase (1974 to 2014), Pubmed, Medline (Ovid, 1946 to 2014), PsycINFO (1806 to 2014) and Cochrane Library. The keywords for search were: non cystic fibrosis bronchiectasis/bronchiectasis, quality of life/QOL/HRQOL, health status, well-being, daily living, questionnaire,

validation/validity, psychology and psychometrics. The date of search was the 6th November 2014. The bibliographies from all included manuscripts were used to identify further references. Abstracts with adequate information about study methods and results were considered for inclusion.

**Study selection, data extraction and quality assessment**

After duplicate references were removed, two reviewers independently assessed the studies (in abstract form) against the inclusion criteria. When there was insufficient information available in the abstract, the full text was reviewed. Discrepancies between the reviewers were resolved through discussion and consensus. Two investigators then extracted data from the selected studies including: author, year of publication, aim of the study, sample size, most common aetiology of bronchiectasis, age, gender, $FEV_1$% predicted, HRQOL questionnaire used and psychometric properties of HRQOL questionnaire including correlation of HRQOL with other clinical measures. Clinical measures used for convergent and discriminant validity of HRQOL included those that assessed symptoms, anxiety, depression, exercise capacity, lung function and other physiological parameters and markers of disease severity and infection/exacerbation. The quality of studies was assessed using a critical appraisal tool developed by Swigris et al and modified for bronchiectasis (online supplement Appendix 1).[7] Where translated questionnaires were used, the translation procedure was assessed by evaluating the included study and related references for forward-backward translation, cognitive interviews, floor and ceiling effects, internal consistency and test-retest reliability.

**Statistical analysis**

Quantitative analysis was performed with Stata 12.0 (StataCorp LP, Texas) and MetaWin 2.0 (Baker Hughes Incorporated, Houston). Internal consistency was reported as Cronbach's α

coefficient (acceptable if >0.7) and test-retest reliability as intraclass correlation coefficient (ICC) (moderate if =0.5-0.7 and good if >0.7). Meta-analysis was performed to evaluate the association between HRQOL and clinical measures when data was available from at least two studies. When multiple questionnaires were used to assess HRQOL in the same study, the most relevant to bronchiectasis questionnaire was used in the meta-analysis. When total score was not available, the mean of the domain scores was used. When the same data were repeated in multiple publications, the meta-analysis included the publication with the largest sample size that best met the inclusion criteria.

Correlation coefficients were extracted from the studies when available. The strength of association was categorised as following: weak r <0.4, moderate r=0.4-0.7 and strong >0.7; significance p<0.05). When only p-values and other metrics (t-values, Cohen's d, F values, chi-square values) were available, correlation coefficients were obtained according to formulas suggested by Rosenthal et al.[10] The correlation coefficients were converted to Fisher's Z using $z = 2^{-1} \cdot ln\{(1+r)(1-r)\}$ and subjected to meta-analytic models.[11] For the final interpretation of the findings, a mean r correlation coefficient for associations was calculated from Fisher's Z as per $r = \frac{\exp(2z) - 1}{\exp(2z) + 1} = \tanh(z),$. A random effects model was used to produce a pooled estimate of the correlation coefficients. Statistical heterogeneity was assessed using Cochran's Q test, which examines the null hypothesis that all studies are evaluating the same effect.[12] Statistical significance for heterogeneity was set as $p \leq 0.10$. Heterogeneity was quantified using the $I^2$ statistic, indicating the percentage of total variation across studies that is due to heterogeneity rather than chance.[12] $I^2$ value of 0% was considered to indicate no observed heterogeneity whilst a value >50% substantial heterogeneity.[13-15]

Publication bias was assessed using funnel plots and Rosenthal's fail-safe Number (Rosenthal's N).[16] A funnel plot was created for the clinical measures with more than 10 studies.[17] This is a scatter plot of the effect estimates from individual studies against a measurement of the study's sample size or precision. Resemblance of a symmetrical inverted funnel supports that findings are due to sampling variation alone; thus absence of bias.[18] For the funnel plots indicating publication bias, an Engel's test was performed (null hypothesis: studies are no subject to publication bias, significance $p<0.05$). Rosenthal's N expresses the number of un-retrieved or negative studies that are needed to overturn the results of the meta-analysis and create a non-significant meta-analytic result.

# RESULTS

## Study characteristics

### Study selection

The search retrieved 1,918 publications (online supplement Table E1). Two additional abstracts and a full manuscript were added manually from searching these references.[19-21] A PRISMA flowchart illustrates the studies selection process and reasons for exclusion (Figure 1). Forty-three studies met the inclusion criteria for systematic review, of which 38 were included in the meta-analysis of associations between HRQOL and other clinical measures. Studies with multiple publications were combined and considered as single publications. Five studies had subjects who overlapped with those in other publications.

### Overview of included studies & study quality

The objectives of the included studies are presented in Table 1. All studies were prospective. They all reported cross-sectional findings apart from one,[22] whilst 9 studies also included

longitudinal findings for the investigation of repeatability of the HRQOL questionnaires.[4-6,20,23-27] The studies met a mean (SD) of 48 (14) % of the quality criteria; range 17-78% (Figure 2). No study met the criteria for all quality domains.

Characteristics of patients

Table 1 presents the clinical characteristics of patients. The studies included a total number of 3,727 patients with bronchiectasis (median number of bronchiectasis patients per study 98, range 6-608). The mean study patient age was 59 (range 43-70) years and 64 (range 37-83) % of the patients were female. Three studies recruited participants also during an exacerbation,[28-30] whilst all remaining studies recruited patients during a clinically stable phase.

**Health-related quality of life questionnaires**

Overview of health-related quality of life questionnaires

Seven organ/disease-specific and 2 generic HRQOL questionnaires were identified in the selected studies (Table 1). Fifteen studies administered multiple HRQOL questionnaires. Twenty-seven studies used the SGRQ, 9 the LCQ, 8 the SF-36, 6 the QOL-B Versions 2.0 or 3.0, 2 the Chronic Respiratory Disease Questionnaire (CRDQ), 2 the generic Euro Quality of Life (EuroQOL) and 1 each of the COPD Assessment Tool (CAT), 20-Item Sino-Nasal Outcome Test (SNOT-20) and Cough Quality of Life Questionnaire (CQLQ). A description of these HRQOL questionnaires is given in online supplement Appendix 2. All questionnaires were originally developed in English language. A summary of average HRQOL scores from studies where available is presented in online supplement Table E1.

Validity of translated questionnaires

Eighteen studies used a translated HRQOL questionnaire. Translated SGRQ was used in Spain,[24,31,32] Italy,[31] France,[31] Belgium,[31] Korea,[33] Netherlands,[30] Mexico,[34] Egypt,[35] China,[36] Hong Kong,[23] and Israel;[37] QOL-B in Italy, Belgium, Spain, France and Netherlands;[38] LCQ in Spain,[27] Belgium,[39] Netherlands[30] and Turkey;[40] SF-36 in Spain,[32,41] Netherlands,[30] and Brazil;[3] and CAT in Korea.[33] Eight out of 18 studies reported or referenced a validation of the translated questionnaire. The validation of translated HRQOL questionnaires has been reported for: SGRQ in Mexican,[34] Hong Kong Chinese,[23] Chinese[36] and Korean,[33] LCQ in Spanish,[24] Dutch[42] and Turkish,[43] QOL-B in all aforementioned languages;[44] and SF-36 in Spanish[32,41] and Portuguese Brazilian.[45] These studies validated the translated questionnaires in patients with bronchiectasis, with only exceptions being the Korean SGRQ (range of chronic respiratory diseases);[33] Dutch and Turkish LCQ (chronic cough)[42,43] and the Brazilian SF-36 (COPD and rheumatoid arthritis).[45] One study used factor analysis to demonstrate that the structure of the translated Spanish questionnaire was similar to the original SGRQ.[46]

Floor/ceiling effects and missing data

Floor and ceiling effects and missing data were reported for only 2 HRQOL questionnaires, SGRQ and QOL-B. The floor and ceiling effects for SGRQ in English and Spanish versions were small for all domains (<3%).[4,46] The floor effect for SGRQ Hong-Kong Chinese was <6.4% (activity domain 11.7%) and ceiling effect <1.1%.[23] English and Spanish QOL-B floor effect ranged from 0% to 5.1%, with the exceptions of vitality (7.2%) and physical and social functioning (both 6.4%). The ceiling effects ranged from 0% to 13.5% with exceptions of domains: treatment burden ≤17.4%, social and role functioning ≤21.7%, and emotional functioning ≤24.1%.[5,27,38] Martinez-Garcia et al and Chan et al reported missing data for SGRQ domains with a range 2.0-7.9% and 1.3-7.2% respectively.[23,46] Quittner et al also

reported minimal missing data for QOL-B for all domains with the exception of treatment burden (up to 8.7%).[5,38]

Internal consistency

Cronbach's α coefficients for the HRQOL questionnaires ranged from moderate to high (Table 2). The LCQ had the highest internal consistency (Cronbach's α coefficient 0.91-0.94).[20] QOL-B Cronbach's α coefficients ranged from 0.65 to 0.96,[5,19,26,27] SGRQ from 0.59 to 0.92,[4,23,46] SF-36 from 0.75 to 0.91[41] and CAT was 0.84.[33] The internal consistency of other questionnaires was not reported.

Test-retest reliability

Test-retest reliability data was available for SGRQ, QOL-B and LCQ. ICC was moderate to high (Table 2). The SGRQ was slightly more repeatable over 2 weeks than the QOL-B (ICC range 0.89-0.97 vs. 0.67-0.88 respectively).[4,5,19,23,27,38] The LCQ was highly repeatable over 6 months (ICC=0.96).[6]

Associations between health-related quality of life questionnaires

Several studies reported the strength of association between HRQOL questionnaires. The correlation coefficients ranged from weak to strong. The SGRQ total score correlated with CAT,[31] SNOT-20 and LCQ[6,20] ($r=0.72$, $r=0.72$ and $\rho=-0.70$ respectively, all $p<0.01$). SGRQ total correlated weakly to moderately with SF-36 Physical (range $r=-0.35$ to $-0.68$, $p<0.01$)[4,23] and QOL-B V2.0/V3.0 (range $r=-0.34$ to $-0.81$, $p<0.01$).[5,19,27] The LCQ correlated strongly with SGRQ ($\rho=-0.70$, $p<0.01$) and CQLQ ($r=-0.88$, $p<0.001$)[47] and moderately with CRDQ total ($r=0.51$, $p<0.01$)[47] and EuroQOL ($r=0.52$ to $0.67$, $p<0.001$).[48] The correlation between QOL-B domains and EuroQOL was weak to moderate ($r=0.29$ to $0.66$, $p<0.001$).

Discriminant ability of health-related quality of life questionnaires

SGRQ was reported to be able to discriminate subjects based on the severity of dyspnoea[4,46] and wheeze,[4] sputum volume,[23,46] CT scan extent of bronchiectasis,[49] exacerbation frequency,[4,31,46] presence of sputum colonisation by Pseudomonas Aeruginosa,[46] history of haemoptysis in past year[27] and the bronchiectasis severity index.[31] SGRQ total scores were able to discriminate $FEV_1$% categories.[46] There were conflicting data for the discriminative ability of the QOL-B for impairment in $FEV_1$%. The number of QOL-B domains able to discriminate patients on the basis of $FEV_1$% ranged from 1 to all 8 domains.[5,27,38] QOL-B was however reported to be able to discriminate patients according to CT scan extent of bronchiectasis[27] and sputum Pseudomonas and Haemophilus Influenza colonisation.

**Associations between health-related quality of life and clinical measures: a meta-analysis**

The associations between HRQOL and other clinical measures (convergent/discriminant validity) reported in studies were evaluated in a meta-analysis (Table 3). The associations for clinical measures where only single studies were available are presented in online supplement Table E3. A wide range of associations between HRQOL and clinical measures were reported (Figures 3-6 and online supplement Figures E1-E14). The strongest associations of HRQOL were with respiratory symptoms such as cough (Figure 3), dyspnoea (Figure 4) and fatigue (online supplement Figure E2) and for objective measures with exercise capacity (Figure 5), where there were moderate correlations. There was a weak association between HRQOL and sputum volume (online supplement Figure E4) and microbiological colonisation (online supplement Figure E13), lung function (Figure 6), exacerbation rate (online supplement Figure E10) and extent of bronchiectasis on CT scans (online supplement Figure E6).

Analysis of publication bias & heterogeneity

Publication bias was assessed with a funnel plot for $FEV_1$% predicted and exercise capacity as these were parameters with ≥10 studies available (online supplement Figures E15 and E16). $FEV_1$% resembled a symmetric image, suggesting no publication bias. Exercise capacity funnel had slight asymmetry suggesting possibility of publication bias. However, this was not confirmed with Enger's test (p=0.189).

## DISCUSSION

This is the first systematic review of the psychometric properties of HRQOL questionnaires used to assess bronchiectasis. The review included 43 studies that investigated 3,727 patients. Nine HRQOL questionnaires were identified; the most widely used were the SGRQ and the LCQ. One bronchiectasis-specific questionnaire was identified, the recently published QOL-B. Most HRQOL questionnaires had good internal consistency, test-retest reliability and convergent validity. As expected, there was a stronger association between HRQOL and subjective outcome measures, compared to objective outcome measures, such as $FEV_1$. This suggests that HRQOL questionnaires capture a unique aspect of the illness.

The strongest association of HRQOL was, unsurprisingly, with respiratory symptoms. The best association was with cough, a key symptom of bronchiectasis, in the acute and chronic phase of illness. There were also significant associations with dyspnoea and wheeze. It should be noted that only 2 studies reported the association with cough and wheeze, in contrast to 7 studies for dyspnoea. The review also highlights a potentially important association between HRQOL and fatigue. Fatigue is an recognised symptom of bronchiectasis but its mechanism is poorly understood.[40] There was a moderate association

between HRQOL and symptoms of depression, and a weaker association with anxiety. There was a poor association between HRQOL and frequency of acute exacerbations. This may be because HRQOL was assessed in a stable phase in most studies. Another explanation may be the variability of the definitions of exacerbation used by investigators. The difficulty in defining and reporting exacerbations is well recognised.[50] There was no association between the presence of co-morbidities and HRQOL. This finding is expected because the HRQOL questionnaires used in studies where co-morbidities were reported were the respiratory condition-specific tools SGRQ and QOL-B.

We found a poor association between HRQOL and objective measures of bronchiectasis. The best association of all objective measures identified was with exercise capacity, such as the six-minute walk test. This is not surprising, since measures of exercise capacity are more likely to relate to functional ability than other objective disease outcome measures. This may be of importance for studies investigating the effects of pulmonary rehabilitation. Our findings highlight the discordance between patient-reported outcome measures and physiological measures. There was a poor relationship with lung function measure, $FEV_1$. This is a widely used outcome measure of bronchiectasis. The poor association with HRQOL is consistent with that reported for other chronic respiratory disorders, such as COPD, interstitial lung disease and chronic cough.[51-53] There were also weaker associations between HRQOL and the extent of bronchiectasis on CT scan, and sputum measures such as volume, colour and bacterial colonisation. Our data suggests that HRQOL questionnaires assess a unique dimension of health, which is distinct from that assessed by objective measures. HRQOL measures should ideally complement objective clinical measures in the assessment of bronchiectasis.

Our systematic review suggests that the questionnaires identified generally had good psychometric properties required to assess HRQOL. We used criteria similar to those defined by McHorley et al to assess psychometric properties.[54] The SGRQ was the most widely studied questionnaire. The SGRQ was initially developed for COPD and asthma,[55] but has subsequently been validated and used in a wide range of respiratory disorders. The next most commonly used tool was the LCQ, which was initially developed for patients with chronic cough,[52] but has subsequently been validated in patients with bronchiectasis.[6] The QOL-B, a recently published questionnaire was the only questionnaire developed specifically for bronchiectasis.[5] The internal consistency and test-retest reliability was generally good for questionnaires studied. The convergent validity was as expected, with a stronger relationship with subjective outcome measures compared to objective measures. The responsiveness of HRQOL questionnaires and their minimal important difference is another important measure of validity. This was beyond the scope of this systematic review, and was therefore not investigated. A review of longitudinal studies of HRQOL questionnaires in bronchiectasis is needed to assess responsiveness of tools.

Eighteen of the 43 studies used translated questionnaires, in 14 languages. It is essential that HRQOL questionnaires are translated and validated using well-recognised and standardised procedures to ensure that they are appropriately adapted to accommodate cultural differences.[56] This procedure includes forward and backward translations, patient interviews, pilot testing and demonstration of internal reliability. Whilst there were good examples of translated HRQOL questionnaire validity in bronchiectasis, there were many studies where this procedure was either not conducted or reported. The validity of translated questionnaires was best reported for the LCQ and QOL-B, compared to the SGRQ. It is likely that the

translation and validity of the SGRQ may have been performed elsewhere and not reported or referenced within the studies identified in this systematic review.

Our systematic review and meta-analysis identified a range of HRQOL questionnaires used to assess bronchiectasis. There was a wide variation in the number of items in questionnaires. For respiratory-specific HRQOL questionnaires, this ranged from 19 items for the LCQ to 50 items for the SGRQ. The QOL-B, a bronchiectasis-specific HRQOL questionnaire, has 37 items, divided into 8 domains. This questionnaire does not have a total score. All questionnaires, with the exception of the QOL-B, were not developed in bronchiectasis. However, some have subsequently been validated in a bronchiectasis patient population, such as the LCQ and SGRQ.[4,6] An advantage of the QOL-B is that its' items are likely to be more focused and relevant for patients with bronchiectasis. Furthermore, the QOL-B is likely to be more sensitive to change or responsive because it is a condition-specific tool. A large proportion of the validation of the QOL-B was conducted in patients with positive sputum cultures; therefore the performance of this questionnaire should be evaluated in patients unselected for sputum microbiology. In this systematic review, HRQOL questionnaires only correlated moderately with each other, which suggests there are differences in the health domains assessed and multiple questionnaires may be necessary in some studies to assess HRQOL. The floor and ceiling effects of questionnaires were seldom reported, but when reported this effect was minimal, which is desirable for HRQOL questionnaires. The exception to this was ceiling effects with the QOL-B reported in one study, up to 24%.[38] The amount of missing HRQOL data was only presented for the SGRQ and QOL-B, and this was reasonably low, within a range between 1.3-7.9% and 0-8.7% of items respectively. There were some differences in the psychometric properties between HRQOL questionnaires, but these were relatively small. The internal consistency was good for all questionnaires; the

Cronbach's α coefficient was highest for the LCQ. The re-test reliability was high for the LCQ and SGRQ and variable for QOL-B domains, ranging from moderate to good. The convergent validity was also variable for the clinical measures studied. The association with exercise capacity was marginally better with SGRQ and LCQ questionnaires compared to QOL-B. The association between HRQOL with $FEV_1$ was generally weak, irrespective of the questionnaire administered. The association with symptoms of dyspnoea was stronger with the SGRQ compared to the QOL-B. It is possible that the differences in psychometric properties may reflect differences in the study population, disease characteristics and methodology undertaken. Studies that directly compare HRQOL questionnaires are needed to establish similarities and differences between questionnaires with confidence.

There are some limitations with our systematic review. Only English-language studies were included. Our review is susceptible to publication bias (positive findings are more likely to be published compared to negative findings) and time lag bias (inability to identify ongoing or unpublished studies), as any review article. Our systematic review and meta-analysis did however involve a comprehensive literature search, which led to the identification of 43 studies for inclusion. We did not contact the study authors to retrieve unpublished data, which may lead to over-interpretation of associations between HRQOL and clinical measures. We chose to limit the review to those studies specifically evaluating the psychometric properties of HRQOL questionnaires and associations with clinical measures. We did not include clinical trials as these studies did not specifically evaluate psychometric validity of questionnaires and this was also beyond the scope of our review. The data available for our systematic review was insufficiently powered to allow assessment of individual clinical outcome measures, for example 6 minute walk test vs. shuttle walk test used to assess exercise capacity. For the purpose of analysis, we grouped clinical measures

together. We therefore may have underestimated important associations due to the heterogeneity of clinical outcome measures. Similarly, we assessed some HRQOL associations by pooling all available HRQOL questionnaires, as there was insufficient data for individual questionnaires. Other potential sources for heterogeneity found in some of the meta-analyses were differences in inclusion/exclusion criteria, population and disease aetiology.

The quality of HRQOL data and its reporting varied between studies. The 43 studies met an average of 48% of the quality criteria assessed. This is very similar to a systematic review of HRQOL in idiopathic pulmonary fibrosis.[7] A greater proportion of studies met quality criteria relating to description of patient demographics, the reporting of major clinical outcome measures of bronchiectasis and the analysis of HRQOL data. Fewer studies met the criteria for reporting details of the administration of the HRQOL questionnaires and missing data. It is therefore possible that the quality of studies and the reporting of data may have compromised some of our findings. A greater clarity for reporting HRQOL data is required in future studies that include the rationale for choosing a particular instrument, mode of administration, details of missing data and sample size estimates.

Our review highlights the questionnaire options available (including translated questionnaires), differences in the size and format of questionnaires and also provides an indication of the relative psychometric properties of questionnaires. The SGRQ, LCQ, QOL-B and SF-36 are the most studied HRQOL questionnaires in bronchiectasis. The SGRQ is a good choice for a research study if extensive experience of using a HRQOL questionnaire is important. The SGRQ also has good psychometric validity. The disadvantage is that it is a long questionnaire and potentially may not be as responsive to change as disease specific

tools; this requires further study. The LCQ is brief, well validated in bronchiectasis and may be particularly advantageous if the symptom of cough is a primary focus. The QOL-B is the only disease specific questionnaire and has good psychometric properties. The disadvantage of the QOL-B is that it is relatively long and does not have a total score for ease of interpretation of data. The SF-36 may be useful in comparative studies that include non-pulmonary chronic disorders, as it is a generic tool. It is however a relatively long questionnaire and is not as extensively validated in bronchiectasis as some of the alternatives. Future studies need to provide details of HRQOL questionnaire performance characteristics, such as the distribution of data, floor and ceiling effects and missing data. There is a need to investigate HRQOL in longitudinal studies, and establish the minimal important difference for many tools used in bronchiectasis. There is also a need for briefer tools with simplified scoring (ideally inclusive of a total score) for use in the clinical and research setting. HRQOL questionnaires should be used to measure the efficacy of therapeutic interventions since they assess the patient's perspective and this should be done in combination with objective outcome measures.

In conclusion, we identified 43 studies that evaluated the psychometric properties of 9 HRQOL questionnaires, and their association with clinical measures. Translated HRQOL questionnaires should be developed using standardised procedures and appropriately validated. This should be reported or referenced. Most HRQOL questionnaires used in bronchiectasis had good psychometric properties. There were some differences between questionnaires in their association with clinical measures. Investigators should select the questionnaires for their study based on ease of administration, and those that correlate best with the health domain under investigation. More research is needed to investigate

longitudinal changes in HRQOL and establish the minimal important differences of instruments.

**Acknowledgements:** We would like to thank Mr A. Drongitis for his assistance in reviewing the papers for inclusion.

**Competing interests:** None of the authors has a financial relationship with a commercial entity that has an interest in the subject of this manuscript. Arietta Spinou is completing a PhD that was financially supported by Greek State Scholarships Foundation (IKY). Surinder S. Birring is a developer of HRQOL tools. Professor R. Wilson and Dr M. Loebinger were co-authors of studies included in the review.

**Funding:** None.

**Contributions:** Conception: AS, RG, SB; Study design: all; Data collection: AS, CF; Analysis and interpretation: all; Wrote the manuscript: AS, SB; Revised and approved the manuscript: all.

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## Table Legends

**Table 1.** Characteristics of studies included in the literature review.

**Table 2.** Internal consistency and test-retest reliability of health-related quality of life questionnaires in non-cystic fibrosis bronchiectasis.

**Table 3.** Meta-analysis: correlations reported for health-related quality of life with clinical measures.

**Table 1.** Characteristics of studies included in the literature review.

| Author 1st, year | HRQOL tools | Country | N | Age (yr) | Female (%) | $FEV_1$% (pred) | Most common bronchiectasis aetiology (%) | Relevant study objectives |
|---|---|---|---|---|---|---|---|---|
| Wilson, 1997a[4] & O'Leary, 2002[57] | SGRQ, SF36 | UK | 111 | 52 | 60 | 66.4 | Idiopathic 58 | Validate SGRQ in bronchiectasis. Relationship between HRQOL, anxiety and depression. |
| Wilson, 1997b[49] & Wilson, 1998[58] | SGRQ, SF36 | UK | 87 | 54 | 56 | 63.8 | Idiopathic 63 | Relationship between HRQOL, sputum bacteriology and systemic inflammatory markers. |
| Chan, 2002[23] | SGRQ, SF36 | HK | 93 | 59 | 66 | 73.5 | Idiopathic 81 | Validate Hong Kong Chinese version of SGRQ. |
| Martinez-Garcia, 2005a[2] & 2005b[46] | SGRQ | ES | 102 | 70 | 37 | 60.4 | Idiopathic 44 | Validate SGRQ in bronchiectasis. Relationship between HRQOL and clinical outcomes. |
| Eshed, 2007[37] | SGRQ | IL | 46 | 63 | 54 | 72.3 | NR | Relationship between SGRQ and CT scores. |
| Tomkinson, 2009[21] | SGRQ | UK | 6 | *59 | 83 | *50.5 | NR | Relationship between HRQOL and exercise capacity. |
| Guilemany, 2009[32] | SGRQ, SF36, SNOT-20 | ES | 80 | 57 | 71 | 80.8 | NR | Relationship between HRQOL and chronic rhinosinusitis. |
| Lee, 2009[59] | SGRQ, SF36 | AU | 27 | 54 | 59 | 73.9 | Post-infective 47 | Relationship between HRQOL and exercise capacity. |
| Shoemark, 2011[60] | SGRQ | UK | 53 | 57 | 71 | *82.1 | NR | Relationship between HRQOL and exhaled nitric oxide. |
| Gale, 2010[61] | SGRQ | UK | 20 | *65 | 80 | 67.8 | NR | Relationship between HRQOL, fatigue, balance and self-reported physical activity. |
| Batchelor, 2011[62] | SGRQ | UK | 31 | 59 | 81 | NR | Post-infective 48 | Relationship between HRQOL, exacerbation frequency, depression, fatigue and lung function. |
| Chalmers, 2014[31] | SGRQ | UK, BE, IT | 608 | 65 | 60 | 69.3 | Idiopathic & Post-infective 63 | Relationship between HRQOL and Bronchiectasis Severity Index. |
| Galindo, 2013[34] | SGRQ | MX | 19 | NR | 74 | NR | CVID 100 | Relationship between HRQOL and sex. |
| Oliveira, 2014a[63] & 2014b[27] | QOL-B(V3.0), SGRQ | ES | 207 | 57 | 63 | 68.3 | Post-infective 39 | Validate QOL-B (V3.0) in Spanish. Relationship between HRQOL, anxiety and depression. |
| Loebinger, 2009[22] | SGRQ | UK | 91 | 52 | 58 | 65.8 | Idiopathic 56 | Relationship between HRQOL and mortality risk. |
| Lee, 2012[33] | CAT, SGRQ | KR | 62 | 61 | 53 | 67.3 | NR | Validate the Korean CAT in bronchiectasis. |
| Moreno, 2013[24] | SGRQ | ES | 70 | 64 | 69 | 74.0 | Idiopathic 46 | Relationship between HRQOL, anxiety and depression. |
| Rowan, 2014[64] | SGRQ | UK | 60 | 62 | 70 | 76.5 | Idiopathic 43 | Relationship between HRQOL and lung clearance index. |
| Gao, 2014[36] | SGRQ | CN | 144 | 46 | 62 | 67.4 | Idiopathic & Post-infective 71 | Relationship between HRQOL and quality of sleep. |
| Morsi, 2014[35] | SGRQ | EG | 33 | 43 | 55 | 32.9 | NR | Relationship between HRQOL, anxiety and depression and other clinical measures. |
| Murray, 2009b[28] | SGRQ | UK | 32 | 69 | 63 | 66.5 | ABPA 34 | Investigate the HRQOL as an end-point for assessing treatment |

| Author 1st, year | HRQOL tools | Country | N | Age (yr) | Female (%) | $FEV_1$% (pred) | Most common bronchiectasis aetiology (%) | Relevant study objectives |
|---|---|---|---|---|---|---|---|---|
| Guilemany, 2006[41] | SF36 | ES | 60 | 52 | 65 | 81.0 | NR | Relationship between HRQOL, nasal symptoms and polyposis. |
| Jacques, 2012[3] | SF36 | BR | 70 | 55 | 69 | 44.9 | Idiopathic 46 | Relationship between HRQOL and exercise capacity. |
| Polley, 2008[48] | LCQ, CQLQ, EuroQOL | UK | 26 | 58 | 50 | 73.2 | NR | Relationship among different HRQOL questionnaires. |
| Ozalp, 2012[40] | LCQ | TR | 20 | 44 | 50 | 62.5 | NR | Relationship between HRQOL and dyspnoea, exercise capacity, fatigue. |
| Murray, 2009a[6] & 2009c[65] | LCQ, SGRQ | UK | 141 | 68 | 64 | 74.0 | Post-infective 53 | Relationship between HRQOL and sputum colour. Validate the LCQ in bronchiectasis. |
| Munoz, 2013[20] | LCQ, SGRQ | ES | 259 | 58 | NR | NR | NR | Validate LCQ Spanish version in bronchiectasis. |
| Altenburg, 2014[30] | LCQ, SGRQ, SF-36 | NL | 60 | 67 | 58 | 82.3 | Idiopathic 50 | Relationship between HRQOL and lower respiratory tract infections visual analogue score. |
| Goeminne, 2014[39] | LCQ | BE | 63 | 59 | 57 | 69.0 | Idiopathic 27 | Relationship between HRQOL, lung function and inflammatory markers. |
| Torrego, 2006[66] | LCQ | UK | 22 | 59 | 82 | 82.9 | NR | Relationship between HRQOL and cough reflex. |
| Mandal, 2013[67] | LCQ | UK | 163 | 66 | 60 | 75.0 | Idiopathic 58 | Relationship between HRQOL and airway reflux. |
| Quittner, 2010b[19] | QOL-B | US | 35 | 65 | 57 | 57.1 | NR | Develop and validate the QOL-B. |
| Quittner, 2010a[26] | QOL-B, SGRQ | US | 79 | 63 | 68 | 60.2 | NR | Validate the QOL-B. |
| McCullough, 2011[68] | QOL-B | UK | 71 | 65 | 69 | 60.0 | NR | Relationship between HRQOL, clinical and demographic factors. |
| Quittner, 2014[5] | QOL-B, SGRQ | US | 89 | 64 | 70 | 60.4 | NR | Develop and validate the QOL-B (V2.0 & V3.0). |
| Quittner, 2015[38] | QOL-B, SGRQ, EuroQOL | US, CA, UK, AU, FR, NL, IT, ES, BE | 542 | 64 | 69 | 63.0 | NR | Validate the QOL-B (V3.0). |
| Lee, 2010[47] | CRDQ, LCQ | AU | 27 | 64 | NR | 70.0 | NR | Relationship between CRDQ, LCQ and exercise capacity. |
| Courtney, 2008[29] | CRDQ | UK | 18 | *54 | 67 | 58.1 | Post-infective 83 | Investigate the impact of physiology and inflammation in changes of HRQOL. |

Data presented as means unless otherwise stated. Studies presented on the same row were combined for meta-analysis.

*: Median. AU: Australia, BE: Belgium, BR: Brazil, CA: Canada, CN: China, CVID: Common Variable Immunodeficiency, EG: Egypt, ES: Spain, FR: France, HK: Hong-Kong, IL: Israel, IT: Italy, KR: Korea, MX: Mexico, NL: Netherlands, TR: Turkey, UK: United Kingdom. ABPA: Allergic Bronchopulmonary Aspergillosis, CAT: Chronic Obstructive Pulmonary Disease Assessment Tool, CRDQ: Chronic Respiratory Questionnaire, EuroQOL: Euro Quality of Life, HRQOL: Health Related Quality of Life, LCQ: Leicester Cough Questionnaire, NR: not reported, SF-36: Short Form 36, SGRQ: St George's Respiratory Questionnaire, SNOT-20: Sinonasal Outcome Test-20, QOL-B: Quality of Life - Bronchiectasis.

**Table 2.** Internal consistency and test-retest reliability of health-related quality of life questionnaires in non-cystic fibrosis bronchiectasis.

| Author, year | HRQOL questionnaire | Internal consistency | | Test-retest reliability | |
|---|---|---|---|---|---|
| | | **Domain** | **Cronbach's α** | **Domain** | **ICC** |
| Wilson, 1997[4] | SGRQ | Total | NR | Total | 0.97 |
| | | Symptoms | 0.90 | Symptoms | 0.93 |
| | | Activity | 0.89 | Activity | 0.98 |
| | | Impact | 0.92 | Impact | 0.94 |
| Martinez-Garcia, 2005[46] | SGRQ | Total | 0.90 | Total | NR |
| | | Symptoms | 0.81 | Symptoms | NR |
| | | Activity | 0.87 | Activity | NR |
| | | Impact | 0.81 | Impact | NR |
| Chan, 2002[23] | SGRQ | Total | 0.92 | Total | 0.93 |
| | | Symptoms | 0.59 | Symptoms | 0.94 |
| | | Activity | 0.91 | Activity | 0.84 |
| | | Impact | 0.88 | Impact | 0.89 |
| Quittner, 2010b[26] | QOL-B | 8 domains | (range) 0.65-0.94 | 8 domains | (range) 0.72-0.88 |
| Quittner, 2010a[19] | QOL-B | 8 domains | (range) 0.73-0.96 | 8 domains | NR |
| Quittner, 2014[5] | QOL-B V3.0* | Physical functioning | 0.94 | Physical functioning | 0.88 |
| | | Role functioning | 0.86 | Role functioning | 0.84 |
| | | Vitality | 0.85 | Vitality | 0.67 |
| | | Emotional functioning | 0.72 | Emotional functioning | 0.82 |
| | | Social functioning | 0.66 | Social functioning | 0.85 |
| | | Treatment burden | 0.84 | Treatment burden | 0.76 |
| | | Health perceptions | 0.77 | Health perceptions | 0.78 |
| | | Respiratory symptoms | 0.82 | Respiratory symptoms | 0.80 |
| Quittner, 2015[38] | QOL-B V3.0 | Physical functioning | 0.91 | Physical functioning | 0.85 |
| | | Role functioning | 0.84 | Role functioning | 0.86 |
| | | Vitality | 0.73 | Vitality | 0.74 |
| | | Emotional functioning | 0.83 | Emotional functioning | 0.79 |
| | | Social functioning | 0.77 | Social functioning | 0.80 |
| | | Treatment burden | 0.78 | Treatment burden | 0.76 |
| | | Health perceptions | 0.77 | Health perceptions | 0.76 |
| | | Respiratory symptoms | 0.81 | Respiratory symptoms | 0.83 |
| Olveira, 2014[27] | QOL-B V3.0 | Physical functioning | 0.91 | Physical functioning | 0.88 |
| | | Role functioning | 0.84 | Role functioning | 0.86 |
| | | Vitality | 0.82 | Vitality | 0.78 |
| | | Emotional functioning | 0.84 | Emotional functioning | 0.86 |
| | | Social functioning | 0.70 | Social functioning | 0.78 |
| | | Treatment burden | 0.72 | Treatment burden | 0.68 |
| | | Health perceptions | 0.71 | Health perceptions | 0.83 |
| | | Respiratory symptoms | 0.87 | Respiratory symptoms | 0.83 |
| Murray, 2009[6] | LCQ | Total | NR | Total | 0.96 |
| | | Physical | NR | Physical | NR |
| | | Psychological | NR | Psychological | NR |
| | | Social | NR | Social | NR |
| Munoz, 2013[20] | LCQ | Total | 0.91 | Total | NR |
| | | Physical | 0.94 | Physical | NR |
| | | Psychological | 0.93 | Psychological | NR |
| | | Social | 0.93 | Social | NR |
| Lee, 2012[33] | CAT | Total | 0.84 | Total | NR |
| Guilemany, 2006[41] | SF36 | 8 domains | (range) 0.75-0.91 | | NR |

Cronbach's α coefficient >0.7 is considered acceptable for HRQOL questionnaires.

CAT: Chronic Obstructive Pulmonary Disease Assessment Tool, HRQOL: Health-Related Quality of Life, ICC: Intraclass Correlation Coefficient, LCQ: Leicester Cough Questionnaire, NR: not reported, SGRQ: St George's Respiratory Questionnaire, QOL-B: Quality of Life - Bronchiectasis.

*: The repeatability of Quality of Life - Bronchiectasis Version 3.0 was not reported. Table presents data from Quality of Life - Bronchiectasis Version 2.0.[5]

**Table 3.** Meta-analysis: correlations reported for health-related quality of life with clinical measures.

| Clinical Measures | K | N | Meta-analysis correlation mean r (95% CI) | | | | Q test | | $I^2$ (%) | Rosenthal's N |
|---|---|---|---|---|---|---|---|---|---|---|
| Cough | 2 | 124 | 0.57 | (-0.03, | 0.87); | p=0.060 | 7.56; | p=0.006 | 86.8‡ | 20# |
| Dyspnoea | 7 | 1216 | 0.55 | ( 0.41, | 0.68); | p=0.000 | 54.42; | p=0.000 | 89.0‡ | 792 |
| Wheeze | 2 | 213 | 0.42 | ( 0.30, | 0.53); | p=0.000 | 0.27; | p=0.602 | 0.0 | 29 |
| Fatigue | 4 | 182 | 0.42 | ( 0.23, | 0.58); | p=0.000 | 4.72; | p=0.194 | 36.4 | 40 |
| Exercise capacity | 11 | 1038 | -0.41 | (-0.54, | -0.24); | p=0.000 | 50.81; | p=0.000 | 80.3‡ | 419 |
| Depression | 7 | 572 | 0.41 | ( 0.23, | 0.55); | p=0.000 | 27.53; | p=0.000 | 78.2‡ | 220 |
| Sputum volume | 3 | 402 | 0.36 | ( 0.24, | 0.47); | p=0.000 | 3.39; | p=0.184 | 41.0 | 57 |
| Pseudomonas presence/colonisation | 2 | 189 | 0.36 | ( 0.23, | 0.48); | p=0.000 | 0.70; | p=0.401 | 0.0 | 18# |
| CT bronchiectasis scores | 10 | 1880 | 0.35 | ( 0.05, | 0.58); | p=0.002 | 340.27; | p=0.000 | 97.4‡ | 1037 |
| Oxygen saturation | 4 | 324 | -0.35 | (-0.44, | -0.24); | p=0.000 | 0.46; | p=0.928 | 0.0 | 51 |
| Anxiety | 5 | 514 | 0.34 | ( 0.19, | 0.47); | p=0.025 | 11.38; | p=0.023 | 64.9† | 97 |
| Hospital admissions rate | 2 | 695 | 0.34 | ( 0.16, | 0.49); | p=0.000 | 2.95; | p=0.086 | 66.1† | 55 |
| FEV1 % | 17 | 2228 | -0.31 | (-0.40, | -0.23); | p=0.000 | 59.32; | p=0.000 | 73.0† | 990 |
| Infections/exacerbations rate | 8 | 1498 | 0.31 | ( 0.24, | 0.38); | p=0.001 | 12.99; | p=0.072 | 46.1 | 380 |
| FVC % | 7 | 1031 | -0.29 | (-0.39, | -0.19); | p=0.000 | 14.39; | p=0.026 | 58.3† | 182 |
| Any microbiological presence/colonisation | 3 | 758 | 0.26 | ( 0.19, | 0.33); | p=0.000 | 0.43; | p=0.805 | 0.0 | 43 |
| Sputum colour | 2 | 204 | 0.25 | ( 0.05, | 0.43); | p=0.013 | 1.91; | p=0.167 | 47.6 | 7# |
| Comorbidities | 2 | 815 | 0.09 | ( 0.02, | 0.16); | p=0.014 | 0.44; | p=0.508 | 0.0 | 3# |

CI: confidence intervals, CT: computed tomography, FVC%: forced vital capacity percent predicted, $FEV_1$%: forced expiratory volume in the first second percent predicted, K: number of studies, N: number of overall participants, r: correlation coefficient.

For the purposes of comparison, higher score indicates poorer health-related quality of life.

Statistical heterogeneity among the studies was assessed using the Q test and quantified using the $I^2$.

Q: Cochran's Q test, which examines the null hypothesis that all studies are evaluating the same effect.

$I^2$: Indicates the percentage of total variation across studies that is due to heterogeneity rather than chance. $I^2$ value of 0% was considered to indicate no observed heterogeneity. †: $I^2$ between 30-60% may represent moderate heterogeneity among the studies according to Cochrane manual; ‡: $I^2$ between 75-100% may represent considerable heterogeneity.

#: Rosenthal's Number lower than $5*k_{number\_of\_studies} + 10$ indicates publication bias of the studies included in the meta-analysis.

## FIGURE LEGENDS

**Figure 1.** PRISMA flowchart of the literature review and meta-analysis selection process.

**Figure 2.** Estimated quality of reporting for included studies.

**Figure 3.** Forest plot for the correlation between health-related quality of life and cough.

**Figure 4.** Forest plot for the correlation between health-related quality of life and dyspnoea.

**Figure 5.** Forest plot for the correlation between health-related quality of life and exercise capacity.

**Figure 6.** Forest plot for the correlation between health-related quality of life and $FEV_1$% predicted.

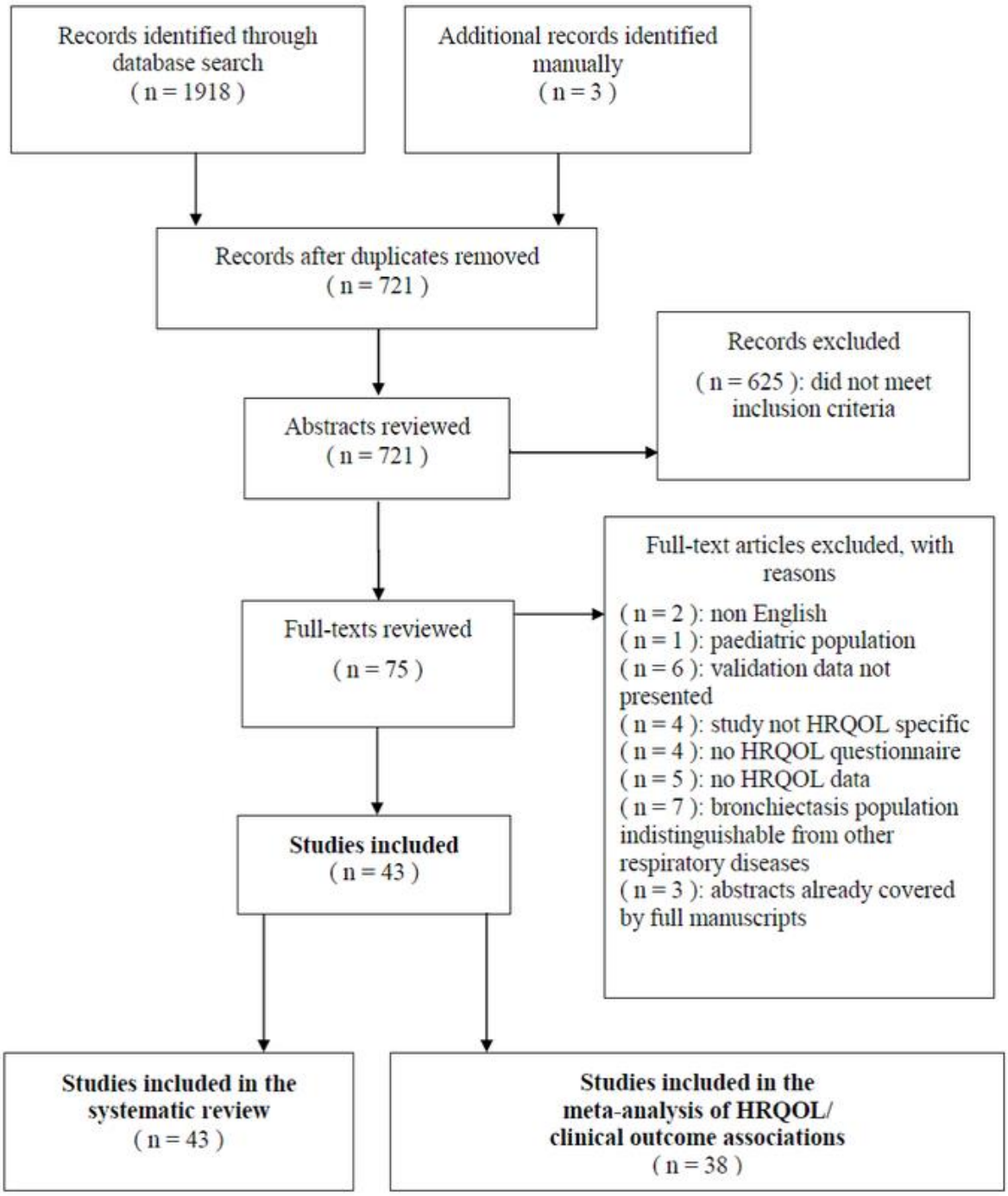


**Figure 1.** PRISMA flow chart of the literature review and meta-analysis selection process. HRQOL, health-related quality of life.

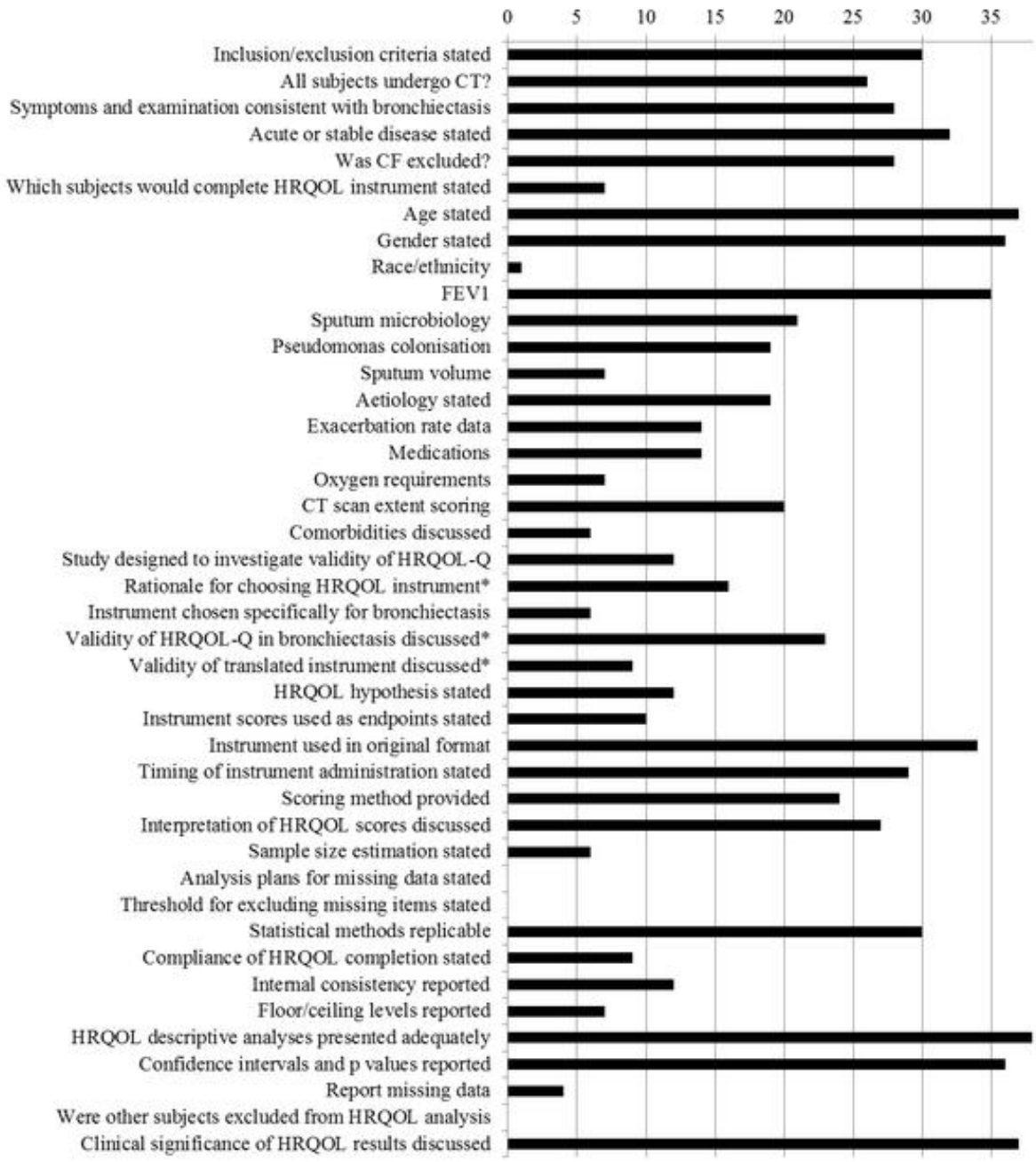


**Figure 2.** Estimated quality of reporting for included studies.

x axis: number of studies meeting each quality criterion (total n=43), y axis: quality criterion item. Number of total evaluable studies 43 except where indicated as*.

CF, cystic fibrosis; CT, computed tomography; HRQOL, health-related quality of life; HRQOL-Q, health-related quality of life questionnaire.

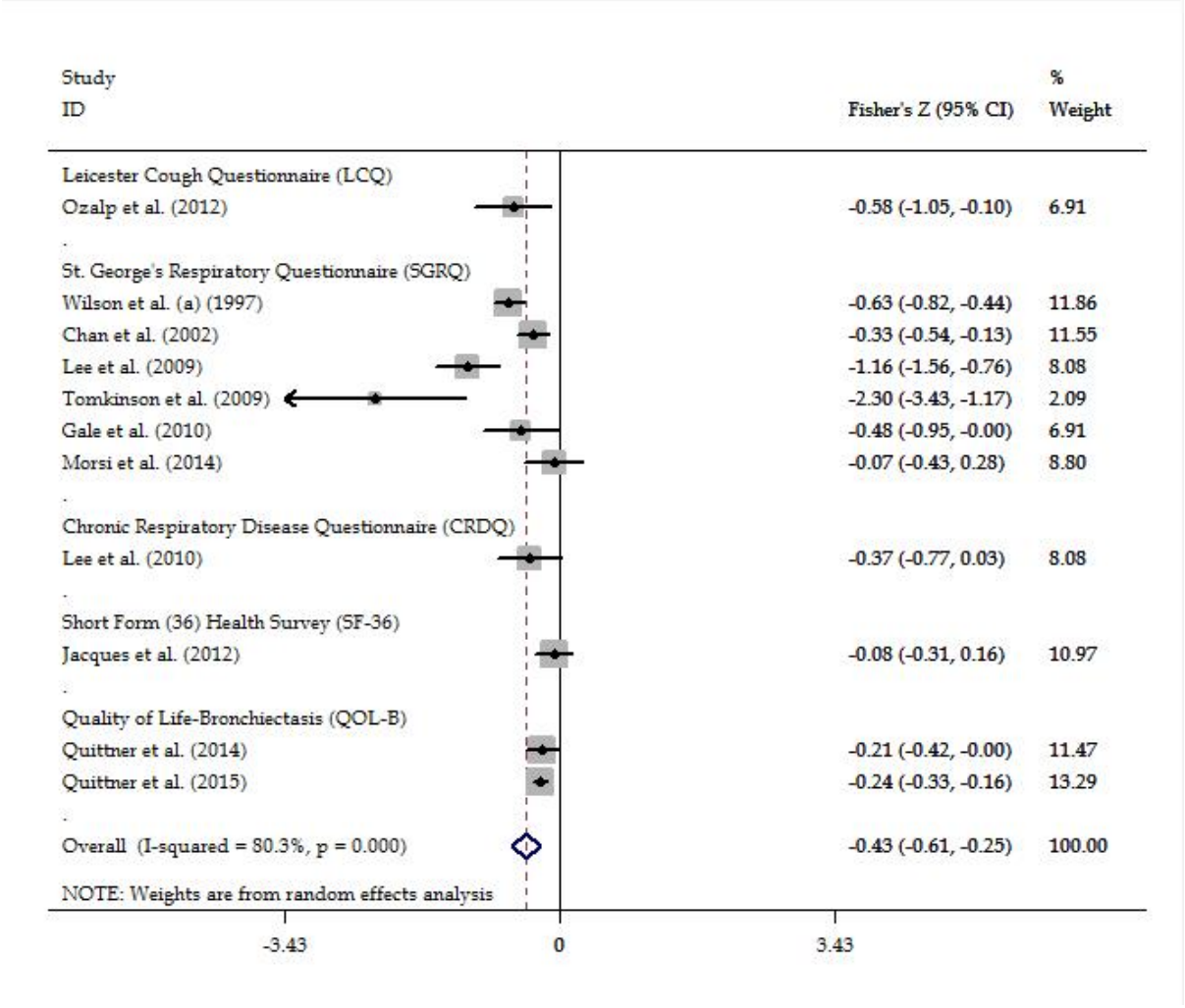


**Figure 3.** Forest plot for the correlation between health-related quality of life and dyspnoea. Measurements of dyspnoea used: Medical Research Council (MRC) scale (Wilson et al, 1997; Martinez-Garcia et al, 2005; Lee et al, 2012; Chalmers et al, 2014; Oliveira et al, 2014), 12-point Borg scale (Chan et al, 2002) and dyspnoea-12 (Morsi et al, 2014).

Zero line: is illustrated to indicate the direction of association. A fisher's z value >0 indicates positive association between the two variables. A fisher's z value <0 indicates negative association between the two variables. High score = poor health-related quality of life. Dashed line: represents the overall meta-analytic mean Z. Arrow: indicates confidence interval limit. Weight was calculated using the inverse variance weight formula [weight=i/sqrt(n-3)].

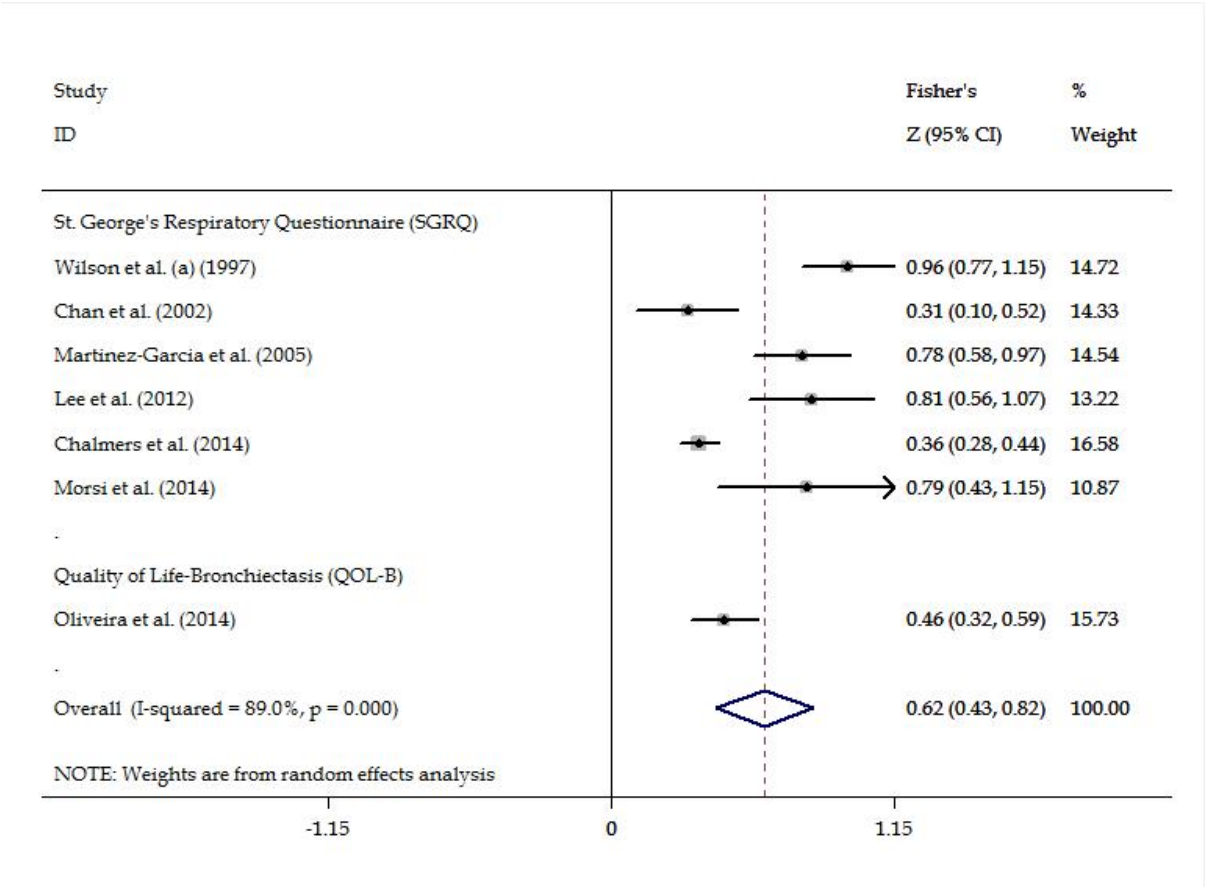


**Figure 4.** Forest plot for the correlation between health-related quality of life and exercise capacity. Measurements of exercise capacity used: 6-minute walk test for all studies apart from one that used incremental shuttle walk test (Wilson et al, 1997) and another that used both (Lee et al, 2010).

High score = poor health-related quality of life.

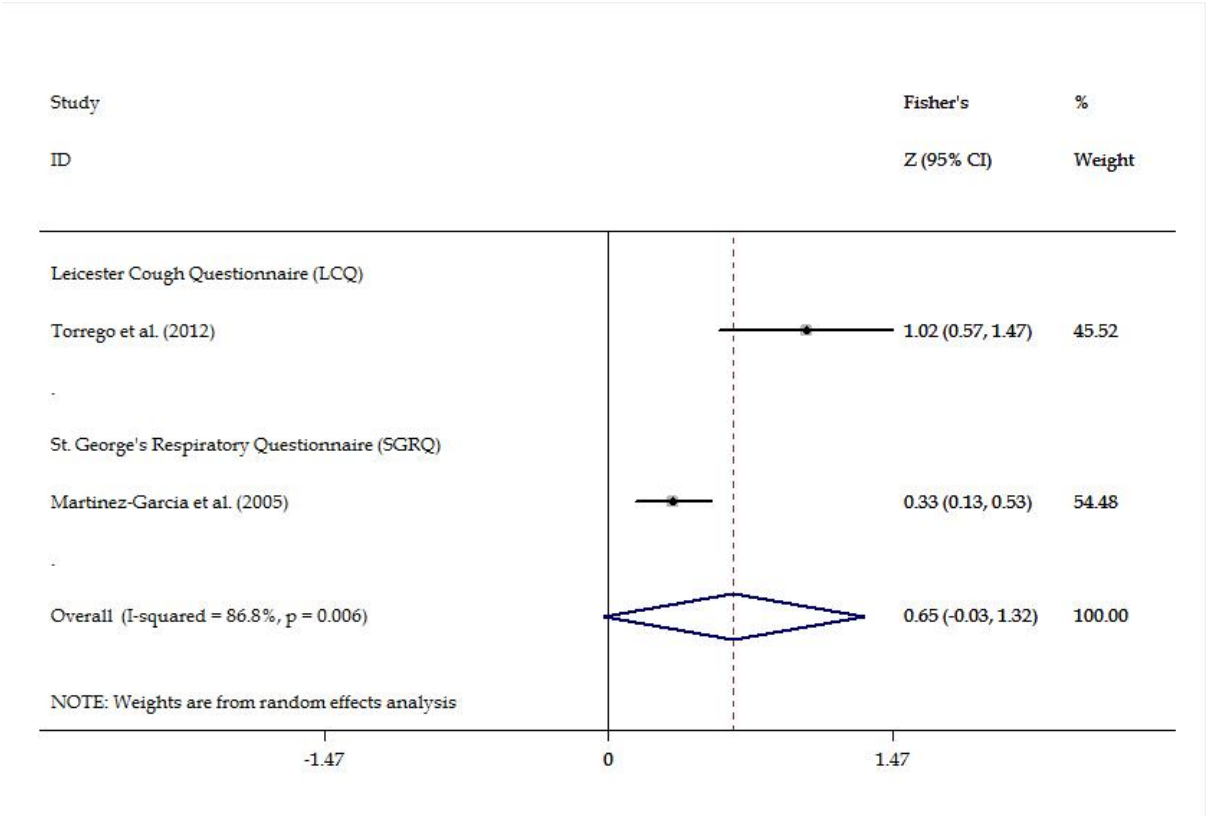


**Figure 5.** Forest plot for the correlation between health-related quality of life and cough. Measurements of cough used: cough reflex sensitivity to capsaicin (Torrego et al, 2006) and patient-reported cough frequency (Martinez-Garcia et al, 2005).

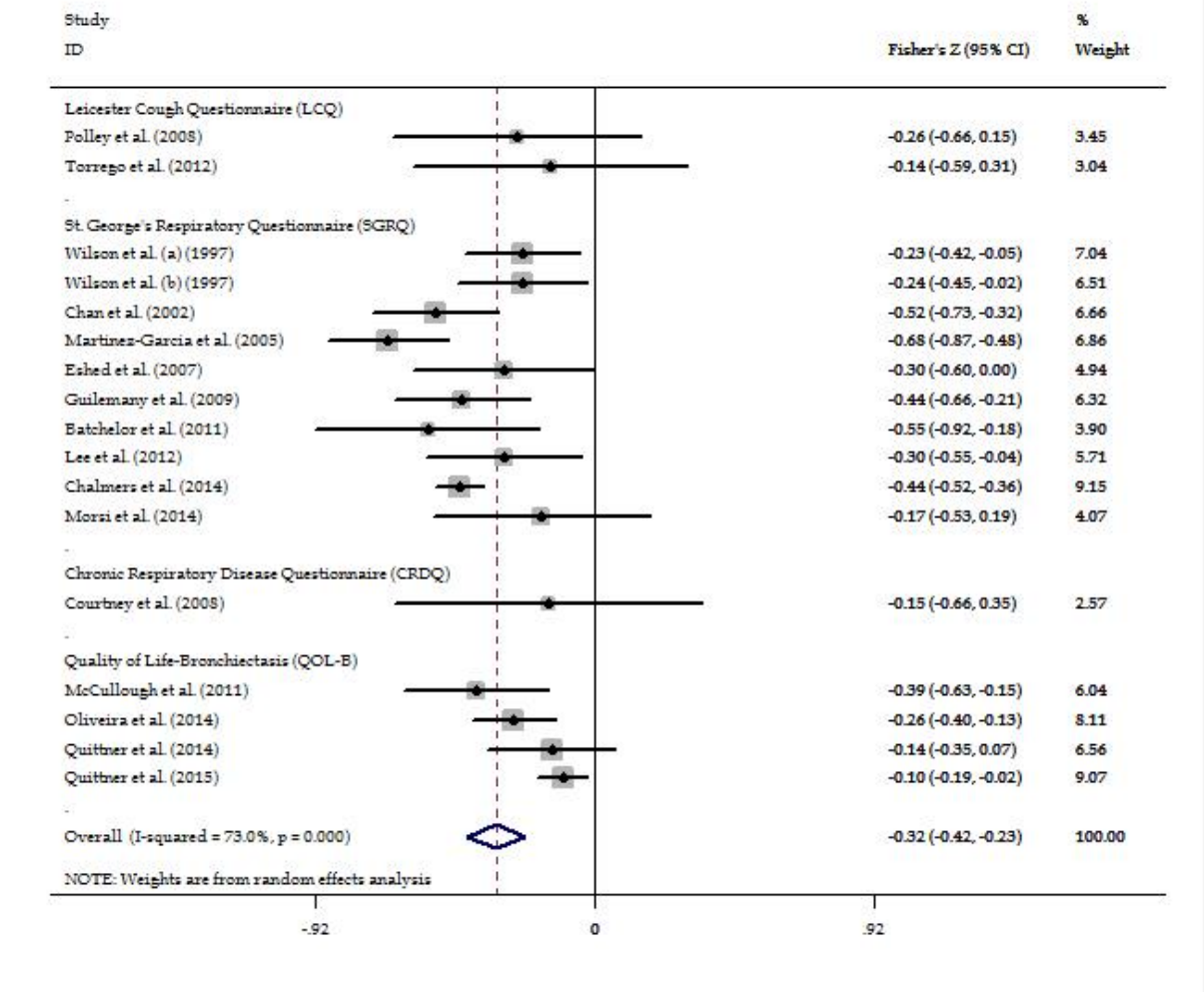


**Figure 6.** Forest plot for the correlation between health-related quality of life and $FEV_1$% predicted.

High score = poor health-related quality of life.